

USSN 09/540,018

- 2 -

Art Unit 1641

constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC₅₀ of $1 \times 10^{-7} \text{ M}$ or less.

B1 cut
3 66. (New) A method for inhibiting human TNF α activity comprising contacting human TNF α with an antibody such that human TNF α activity is inhibited, wherein the antibody is an isolated human antibody, or antigen-binding portion thereof, with the following characteristics:

- a) dissociates from human TNF α with a K_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance;
- b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;
- c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

3 67. (New) A method for inhibiting human TNF α activity comprising contacting human TNF α with an antibody such that human TNF α activity is inhibited, wherein the antibody is an isolated human antibody, or an antigen binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

4 68. (New) A method for inhibiting human TNF α activity in a human subject suffering from a disorder in which TNF α activity is detrimental, comprising administering to the human subject an antibody such that human TNF α activity in the human subject is inhibited, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNF α with a K_d of $1 \times 10^{-8} \text{ M}$ or less and a K_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC₅₀ of $1 \times 10^{-7} \text{ M}$ or less.

*60**B*

USSN 09/540,018

- 3 -

Art Unit: 1641

~~5~~ 69. (New) A method for inhibiting human TNF α activity in a human subject suffering from a disorder in which TNF α activity is detrimental, comprising administering to the human subject an antibody such that human TNF α activity in the human subject is inhibited, wherein the antibody is an isolated human antibody, or antigen-binding portion thereof, with the following characteristics:

- a) dissociates from human TNF α with a K_{off} rate constant of 1×10^{-3} s⁻¹ or less, as determined by surface plasmon resonance;
- b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;
- c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

~~6~~ 70. (New) A method for inhibiting human TNF α activity in a human subject suffering from a disorder in which TNF α activity is detrimental, comprising administering to the human subject an antibody such that human TNF α activity in the human subject is inhibited, wherein the antibody is an isolated human antibody, or an antigen binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

Sub 2

71. (New) The method of claim 70, wherein the disorder is sepsis.

72. (New) The method of claim 71, wherein the antibody is administered to the human subject together with the cytokine interleukin-6 (IL-6) or is administered to a human subject with a serum or plasma concentration of IL-6 above 500 pg/ml.

Sub 3

73. (New) The method of claim 70, wherein the disorder is an autoimmune disease.

61

B

USSN 09/540,018

- 4 -

Art Unit: 1641

74. (New) The method of claim 73, wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and gouty arthritis.

75. (New) The method of claim 73, wherein the autoimmune disease is selected from the group consisting of an allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis and nephrotic syndrome.

76. (New) The method of claim 70, wherein the disorder is an infectious disease.

77. (New) The method of claim 70, wherein the disorder is transplant rejection or graft-versus-host disease.

78. (New) The method of claim 70, wherein the disorder is a malignancy.

79. (New) The method of claim 70, wherein the disorder is a pulmonary disorder.

80. (New) The method of claim 70, wherein the disorder is an intestinal disorder.

81. (New) The method of claim 70, wherein the disorder is a cardiac disorder.

82. (New) The method of claim 70, wherein the disorder is selected from the group consisting of inflammatory bone disorders, bone resorption disease, alcoholic hepatitis, viral hepatitis, coagulation disturbances, burns, reperfusion injury, keloid formation, scar tissue formation and pyrexia.

Sub C4
B1 w/

B